Remarks/arguments

Claims 1, 4 - 8, 17 - 37 are presently in the case. Claims 9-16, 38 and 39 have been canceled without prejudice to filing a continuation directed to the canceled subject matter. Claims 17 - 19 and 20 have been amended to correct claim dependencies. Claims 1, 20, 24, 27 and 37 have been amended to recite that the liposome delivery system is an unpolymerized gel-like lamellar liposome delivery system at room temperature. Support for this amendment can be found in the specification at page 6, line 18 and in Examples 1 and 2 which were conducted at room temperature. Claims 1 and 37 have been amended to indicate that the liposome delivery system comprises lipids and discrete domains of colipids. Support for this amendment can be found in the specification on, for example, page 17, line 26 - page 18, line 6. No new matter is added by the amendment, because the amended application is fully supported by the application as filed. Entry of this amendment is respectfully requested

Interview

Applicants would like to thank the Examiner for the courtesies he extended during the interview on August 10, 2004.

Claim Rejections - 35 USC §112

1. Claim 39 stands rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.

Although Applicants specifically disagree with this rejection, Applicants have canceled Claim 39 without prejudice to filing a continuation directed to the canceled subject matter. Withdrawal of this rejection is respectfully requested.

Claim Rejections - 35 USC §102(b)

Claims 1, 4, 9-11, 16-17, 23, 32 and 33 stand rejected under 35 U.S.C. 102(b) as being anticipated by Lamparski (Biochemistry, vol. 31., 1992). The Examiner alleges that Lamparski discloses liposomes containing a phospholipid and a polymerizable co-lipid.

The subject matter of the independent Claim 1 and Lamparski are different in many aspects.

Applicants Invention

Generally, in order for liposomes to reach the target site in the patient without significant loss of their contents, passive leakage of the contents must be slow relative to the time required for liposomes to circulate and escape the vasculature. It would be desirable to stimulate enhanced release of the encapsulated agent from the liposomes once the liposomes are at the target site or tumor site in a patient.

Applicants have discovered that liposomes can be destabilized and the contents released with ionizing radiation. By selecting certain lipids and ionizing radiation polymerizable colipids, Applicants can generate a liposome in which the colipids in the liposome are clustered in discrete domains in the gel-like lamellar liposome. Applicants have also shown that if the colipids are clustered in discrete domains at the time of ionizing radiation, the ionizing radiation has an effect in destabilizing the liposome, thereby releasing the agents present within the liposome. Accordingly, it is possible to achieve enhanced release of the encapsulated agent from the liposomes once the liposomes are at the target site in the patient. Use of low doses of ionizing radiation is beneficial, because it can penetrate the patient's body and be directed to the site where release of the agent is desired.

The Case Law

MPEP §2131 provides, "'A claim is anticipated only if *each* and *every* element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.[1],. A showing that the prior art reference lack[ed] the characteristics of the claimed invention would in fact negate the assertion that the claimed invention was described in the prior art.[2].

Analysis

Applicants respectfully point out that the global transition temperature (T_M) of the liposomes disclosed in Lamparski are substantially below the room temperature. The liposomes disclosed in Lamparski are in a fluid state at room temperature and are not in a gel-like state.

The Declaration of Dr. O'Brien[3] states that in Lamparski the liposomes were composed of DOPE or DOPC in either a 2:1 or 3:1 molar ratio with bis-SorbPC (para. 6).

> "Therefore, the liposomes prepared and studied in Lamparski were designed to form fluid phase liposomes at room temperature and above. Furthermore, at 3:1 molar ratio with bis-SorbPC, the global transition temperature would have been substantially below the room temperature. These conditions favor random mixing of the lipids and bis-SorbPC where polymerizable colipids are randomly distributed throughout the liposomal membrane."

First Applicants note that David O'Brien is one of the authors of the Lamparski article. Secondly, the liposomes disclosed in Lamparski would not form discrete domains at room temperature. Accordingly, the liposomes taught by Lamparski do not anticipate the claimed invention. In this case, there is no disclosure, either inherent or explicit, in Lamparski which

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1 *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051-1053 (Fed. Cir. 1987)
2 *In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)*
3 The Declaration of Dr. O'Brien was previously filed in this application on June 28, 2002.

would indicate *the colipids are clustered in discrete domains.* Accordingly, Lamparski et al. does not disclose *each* and *every* element as set forth in the claims, either expressly or inherently. The liposomes taught by Lamparski do not anticipate the claimed invention.

Therefore Claim 1 is not anticipated by Lamparski et al. and the Examiner is respectfully requested to reconsider and withdraw the rejection.

Claim Rejections - 35 USC §103(a)

1. Claims 1, 4-5, 9-11, and 16-31-33, 36 and 38-39 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Lamparski in view of either Heldebrant (U.S. Patent No. 5,061,484) or Charych (U.S. Patent No. 6,180,135) in further combination with Hallahan (U.S. Patent No. 6,159,443). It allegedly would have been obvious to use the liposomes of Lamparski for the delivery of the diagnostic or therapeutic agents with a reasonable expectation of success since Lamparski provides guidance as to how to prepare the liposomes and suggests their use.

The Office Action alleges that Lamparski teaches the instant liposomes and the destabilizing effect of ultra-violet light on the liposomal membrane. "What is lacking in Lamparski are the teachings of the use of X-rays for polymerization of the lipids and destabilizing the liposome. Although Lamparski does not specifically teach a method of administration of a therapeutic agent or a diagnostic agent, Lamparski allegedly suggests the applicability of the radiation induced destabilizing of the liposome and the regulation of the release of the biological agents (page 693)."

The Office Action states that Heldebrant allegedly discloses the administration of liposomal composition to tumor bearing mice and teaches that liposomal lipids can be polymerized by either UV radiation or by x-rays.

The Office Action states that Charych allegedly teaches that liposomal lipids can be polymerized by either UV radiation or by X-rays.

The Office Action states that Hallahan allegedly discloses X-ray guided drug delivery to treat various neoplasms.

The Office Action agrees that Lamparski teaches only the application of ultraviolet light as the source for polymerization. However, in the absence of a showing of criticality, the Patent Office deems it obvious to use any form of ionization as long as they polymerize the lipid. The use of X-rays as the ionizing radiation with the liposomes of Lamparski would allegedly have been obvious to one of ordinary skill in the art since X-rays are not only another form of ionizing radiation to polymerize the liposomal lipids as shown by Heldebrant or Charych, but also provide an improved method of delivery when combined with delivery vehicles such as the liposomes shown by Hallahan. Hallahan discloses administering a therapeutic agent or diagnostic agent in a delivery vehicle (liposome) . The liposome also contain antibodies attached to them.

Applicants respectfully disagree.

The Case Law

For the claimed subject matter to be obvious in view of a combination of prior art references, the prior art must suggest the combination to one of ordinary skill in the art and reveal that one of such skill would have a reasonable expectation of success in carrying out the invention[4].

It is impermissible for the Examiner simply to use hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from the references

4 *In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).*

to fill the gaps.[5] There must be a teaching or suggestion in the art to combine the references and a reasonable expectation of success.

Lamparski has already been discussed in the rejection under 35 U.S.C. §102. First, Lamparski does not teach that the colipids should be clustered in discrete domains at the time of polymerization in order to further destabilize the liposomes. Secondly, as the Examiner agreed at page 4, Lamparski does not teach or suggest the use of ionizing radiation to destabilize the liposome. Finally Lamparski does not teach or suggest the liposomes of the claimed invention.

It is incorrect for the Office Action to state on pages 4-5 that Lamparski suggests the applicability of the radiation induced destabilizing of the liposome and the regulation of the release of the biological agents. In this statement the Patent Office is contradicting itself. The Examiner agrees that Lamparski teaches the use of UV light and not the use of ionizing radiation. As one of skill in the art would know, and as set forth in the Declaration by Bruce Bondurant, Ph.D., UV light polymerizes bis-SorbPC$_{17, 17}$ through photo-addition. Ionizing radiation induced polymerization of bis-SorbPC$_{17, 17}$ occurs through radical chain reaction. These chemical reactions are not the same.

Charych teaches polymerized polymeric assemblies (ie. liposomes) which change from a blue to red color when exposed to an analyte as a diagnostic product. In Charych, diacetylene monomers are combined into a liposome and the liposome is polymerized with a UV lamp in vitro. Charych does teach that X-rays are another polymerization means. Charych does not teach the administration of his liposomes to patients. Charych does not teach a mixture of lipids and colipids. Charych does not teach or suggest the benefit of having the colipid form discrete domains before polymerization. Charych does not teach or suggest administration of

5 *In re Gorman* 933 F2d. 982, 18 USPQ2d 1885 (Fed. Cir. 1991)

unpolymerized liposomes to a patient. Charych does not teach or suggest selecting a colipid and lipid such that the colipid would form discrete domains in the unpolymerized liposome when administered to a patient.

Heldebrant teaches a stable perfluorochemical emulsion which comprises perfluorochemical particles in stabilized vesicles. The stabilized vesicles comprise a biocompatible polymer formed by coating the perfluorochemical particles with one or more phospholipid monomers and polymerizing the monomers. The stabilized/polymerized liposome is then administered to a patient. The purpose of the polymerization is to generate more stable emulsions which (1) can withstand higher and longer sterilization temperatures and times, (2) possess greater stability after sterilization with permits longer storage times; and (3) have longer circulating in vivo half-lives. Heldebrant does not teach or suggest selecting a colipid and lipid such that the colipid would form discrete domains in the liposome. Heldebrant does not teach or suggest administering an unpolymerized liposome to a patient. Heldebrant does not teach or suggest releasing the perfluorochemical from the liposome. In fact, Heldebrant specifically teaches away from the claimed invention by indicating that the liposome should be composed of only polymerizable colipids and be completely polymerized before administration to a patient to ensure stability of the polymerized liposome in the patient and to prevent the release of the perfluorochemical (Col. 6, lines 29 - 40).

Hallahan teaches a targeting technique of delivering an active agent to a target tissue, particularly neoplastic tissue. Hallahan teaches the use of ionizing radiation targeted at tumor sites to induce platelet aggregation. Hallahan teaches the attachment of a delivery vehicles to platelets to increase the targeting of the delivery vehicles. One of many different targeting vehicles mentioned by Hallahan are liposomes. Hallahan does not teach or suggest the use of X-

rays to polymerize any type of unpolymerized liposome in the patient. Accordingly, Hallahan does not teach or suggest a liposome comprising a lipid and an ionizing radiation polymerizable colipid which forms discrete domains.

Accordingly, none of the references, either alone or in combination, teach or suggest a gel-like lamellar liposome delivery system at room temperature comprising a lipid and discrete domains of ionizing radiation polymerizable colipid. Contrary to the statements on page 5 of the Office Action it would not have been obvious to use the liposomes of Lamparski for the delivery of diagnostic or therapeutic agents with a reasonable expectation of success. First, Lamparski does not provide guidance on how to prepare the claimed liposomes or suggest their use as a therapeutic or diagnostic agent. The Examiner is requested to point to the section of Lamparski where such guidance and teaching is provided. Secondly, none of the references teach the use of ionizing radiation to destabilize the liposome. While Charych does teach the use of X-rays for the liposomes taught by Charych, , Charych does not teach the liposomes of the invention or the use of X-rays for the polymerization of the liposomes of the invention. Further, Charych does not teach the administration of such liposomes to patients for therapeutic or diagnostic purposes. None of the references teach or suggest, either alone or in combination, the selection of lipids and colipids to form a unpolymerized liposome delivery system which forms discrete domains. Third, Heldebrant specifically teaches away from the claimed invention by indicating that the liposome should be composed of only polymerizable colipids and be completely polymerized before administration to a patient. Finally, Hallahan does not teach anything about the liposome composition except that it should be conjugated to a peptide or antibody which binds platelets. Accordingly, a combination of the cited references would not result in the claimed invention, much less teach or suggest the claimed invention or a reasonable expectation of success.

In addition, none of the references teach or suggest that ionizing radiation energies that are much higher than UV would cause the clustered colipids to polymerize thereby releasing the contents from the liposome. UV radiation excites an electron. On the other hand , ionizing radiation photons in their interaction with matter can result in the complete displacement of an electron. Accordingly, it is not obvious that the claimed liposome delivery system would comprise an ionizing radiation sensitive colipid. Absent such a teaching the claimed invention is not obvious and withdrawal of this rejection is respectfully requested.

The Office Action does not specifically address claims 20, 24 or 27 which are directed to the method claims in this rejection. Absent reasons for the rejection, the Examiner has failed to meet his burden of proving an *prima facie* case of obviousness. Furthermore, for the reasons set forth above, the references alone or together do not teach or suggest the methods of claims 20, 24, or 27.

Withdrawal of this rejection is respectfully requested.

2. Claims 5-8 and 12-15, and 34-35 and 37 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lamparski in view of either Heldebrant ('484 patent"), Charych (the '135 patent") in further combination with Hallahan ("the '443 patent") and further in view of Woodle (BB 1992). The Examiner indicates that what is lacking in Lamparski and the other references already discussed are the teaching of the inclusion of PEG in the liposomal compositions.

This rejection is also respectfully traversed. The teachings of Lamparski, Heldebrant, Charych and Hallahan have already been discussed.

Woodle does teach the use of pegylated lipids in liposomes. Woodle does not teach the selection of lipids and ionizing radiation polymerizable colipids such that the colipids in the

unpolymerized liposome form discrete domains. Absent such a teaching, Woodle does not cure the deficiencies of the other references and the claims are not rendered obvious.

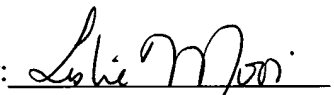
Consequently, there exists no intrinsic basis or extrinsic justification for the proposed combination of Lamparski with Heldebrant, Charych, Hallahan and Woodle and *prima facie* obviousness has not been established. Applicants respectfully traverse the rejection of those claims.

Conclusion

Entry of the amendment, and reexamination, reconsideration, and early allowance of claims 1, 4-8, 17-37 are therefore respectfully requested. Applicants note that the amendments herein do not indicate Applicants' agreement to the propriety of the rejections, and Applicants reserve the right to pursue claims such as those presented previously in a related application.

Please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 08-1641.

Respectfully submitted,

By: 
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